General

Guideline Title

American Gastroenterological Association Institute guideline on the medical management of microscopic colitis.

Bibliographic Source(s)

Nguyen GC, Smalley WE, Vege SS, Carrasco-Labra A, Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the medical management of microscopic colitis. Gastroenterology. 2016 Jan;150(1):242-6. [9 references] PubMed

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Definitions for the quality of evidence (High, Moderate, Low, Very low) and strength of recommendation (Strong, Conditional) are provided at the end of the "Major Recommendations" field.

1. In patients with symptomatic microscopic colitis (MC), the American Gastroenterological Association (AGA) Institute recommends treatment with budesonide over no treatment for the induction of clinical remission. (Strong recommendation, Moderate quality of evidence)
2. In patients with symptomatic MC, the AGA recommends treatment with budesonide over mesalamine for the induction of clinical remission. (Strong recommendation, High quality of evidence)
3. In patients with symptomatic MC in whom budesonide therapy is not feasible, the AGA suggests treatment with mesalamine over no treatment for the induction of clinical remission. (Conditional recommendation, Moderate quality of evidence)
4. In patients with symptomatic MC in whom budesonide therapy is not feasible, the AGA suggests treatment with bismuth salicylate over no treatment for the induction of clinical remission. (Conditional recommendation, Low quality of evidence)
5. In patients with symptomatic MC in whom budesonide therapy is not feasible, the AGA suggests treatment with prednisolone (or prednisone) over no treatment for the induction of clinical remission. (Conditional recommendation, Very low quality of evidence)
6. In patients with symptomatic MC, the AGA suggests against combination therapy with cholestyramine and mesalamine over mesalamine alone for the induction of clinical remission. (Conditional recommendation, Low quality of evidence)
7. In patients with symptomatic MC, the AGA suggests against treatment with Boswellia serrata over no treatment for the induction of clinical remission. (Conditional recommendation, Low quality of evidence)
8. In patients with symptomatic MC, the AGA suggests against treatment with probiotics over no treatment for the induction of clinical remission. (Conditional recommendation, Low quality of evidence)
9. For patients with recurrence of symptoms following discontinuation of induction therapy for MC, the AGA recommends budesonide for

maintenance of clinical remission. (Strong recommendation, Moderate quality of evidence)

Definitions

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality of Evidence

High	The Committee is very confident that the true effect lies close to that of the estimate of the effect.
Moderate	The Committee is moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	The Committee's confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

GRADE Definitions of Strength of Recommendation

	For the Patient	**For the Clinician**
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Clinical Algorithm(s)

An algorithm titled "AGA Institute Guideline on the Management of Microscopic Colitis Clinical Decision Support Tool" is provided (see the "Availability of Companion Documents" field).

Scope

Disease/Condition(s)

Microscopic colitis (MC), comprising two subtypes:

- Collagenous colitis (CC)
- Lymphocytic colitis (LC)

Guideline Category

Management

Treatment

Clinical Specialty

Gastroenterology

Intended Users

Physicians

Guideline Objective(s)

- To present the official recommendations of the American Gastroenterological Association (AGA) Institute on the management of microscopic colitis (MC)
- To reduce practice variation and promote high-value care

Target Population

Adults with microscopic colitis (MC), including patients in remission of symptoms

Interventions and Practices Considered

1. Budesonide
2. Mesalamine
3. Bismuth salicylate
4. Prednisolone (or prednisone)

Note: The following were considered but not recommended: Boswellia serrata, probiotics.

Major Outcomes Considered

- Clinical response
- Histological response
- Quality of life
- Adverse events

Methodology

Methods Used to Collect/Select the Evidence

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

A summary of the focused questions and PICO components is shown in Table 1 of the technical review (see the "Availability of Companion Documents" field).

Definition of the Relative Importance of Outcomes

After defining the included outcomes for each focused question, an online survey was circulated among panel members participating in this review. In this survey, participants were asked to rank the outcomes according to their relative importance. The process was conducted individually and independently. In the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach, the relative importance of an outcome is defined on a scale from 1 (least important) to 9 (most critical); those rated from 1 to 3 are defined as of limited importance, from 4 to 6 as important, and from 7 to 9 as critical. The panel was not aware of the quality of the evidence for each of the outcomes at the moment of assessing their importance. The results of the determination of the relative importance of the outcomes are shown in Table 2 of the systematic review.

Study Selection Criteria and Search Strategy per Question

Question 1. What is the prevalence of microscopic colitis (MC)? How many colon biopsy specimens should be obtained and from which areas of the colon?

Study Selection Criteria

The technical review authors included studies recruiting patients with both lymphocytic colitis (LC) and collagenous colitis (CC). For estimation of the prevalence of the disease, the technical review authors selected studies based on populations of patients with chronic diarrhea. These studies also provided a description of the diagnostic test used, number of biopsy specimens obtained, and areas of the colon from which biopsy specimens were obtained. The technical review authors excluded editorial letters, comments, notes, or case reports.

Search Strategy and Databases

The technical review authors searched Ovid, MEDLINE, Ovid EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), and the Cochrane Database of Systematic Reviews from inception to August 2014. The search strategy included terms such as "microscopic colitis," "colonoscopy," and "biopsy," among others. There was no restriction by language or status of publication.

Question 2. In patients with MC (either LC or CC), which treatments are effective and safe for inducing remission of the disease, measured as clinical response, histological response, quality of life, and adverse events?

Study Selection Criteria

The technical review authors included studies that recruited participants with a confirmed diagnosis of MC, irrespective of whether the patients had CC or LC. In addition, the studies provided information about the effectiveness and safety profile of any medication to treat these conditions compared with other interventions in a head-to-head comparison or placebo. For this question, the technical review authors excluded studies reporting on the effect of interventions for maintaining remission of MC, because these studies are covered in question 3. Given that they were anticipating scarce evidence to answer this question, they included both randomized controlled trials and observational studies during the initial screening process. Good-quality observational studies were included in the review along with the controlled trials.

Search Strategy and Databases

The technical review authors searched Ovid MEDLINE from 1946 to July week 4 2014, Ovid EMBASE from 1980 to 2014 week 31, the Cochrane Central Register of Controlled Trials (CENTRAL) to June 2014, and the Cochrane Database of Systematic Reviews from 2005 to June 2014. The search strategy included terms describing the disease and all medications available for inducing remission of MC. There was no restriction by language. The technical review authors excluded editorial letters, comments, notes, or case reports.

Question 3. In patients successfully treated for MC (either LC or CC) and in remission of symptoms, which treatments are effective and safe for maintaining clinical remission of the disease, measured as maintenance of clinical response, maintenance of histological response, time to relapse, quality of life, and adverse events?

Study Selection Criteria

The technical review authors included treatment trials for patients with a confirmed diagnosis of MC, including both CC and LC, who were in clinical remission. Studies were selected that included information about the effectiveness and safety profile of any medication to maintain remission. They included interventions for maintaining remission compared with other interventions or placebo. They excluded studies reporting on the effect of interventions for inducing remission of MC because those studies were addressed in question 2. Because they anticipated scarce evidence to answer this question, they initially included both randomized controlled trials and observational studies. Good-quality observational studies were included in the review along with the controlled trials.

Search Strategy and Databases

The technical review authors searched Ovid MEDLINE from 1946 to July week 4 2014, Ovid EMBASE from 1980 to 2014 week 31, the Cochrane Central Register of Controlled Trials (CENTRAL) to June 2014, and the Cochrane Database of Systematic Reviews from 2005 to June 2014. The search strategy included terms describing the disease and all medications available for maintaining remission of MC. There was no restriction by language. The technical review authors excluded editorial letters, comments, notes, or case reports.

Study Selection Process

After removing duplicates, 2 researchers independently assessed the retrieved references for eligibility using the title and abstract. References that showed potential eligibility were assessed again in duplicate and independently, this time using full text. A piloted form including the main eligibility

criteria helped to document this process. When there was disagreement, a third person arbitrated to make the final inclusion decision.

For more details about the search strategies, see the appendices in the technical review.

Number of Source Documents

Question 1

The search strategy retrieved 1239 articles, of which 402 were duplicates. The remaining 837 references went to the title and abstract screening stage. Then, 51 were included for full-text screening. A total of 29 primary studies proved eligible (see Figure 1 in the technical review).

Question 2

The search strategy retrieved 592 articles, of which 162 were duplicates. The remaining 430 references went to the title and abstract screening stage. Then, 76 were included for full-text screening. A total of 12 primary studies proved eligible (see Figure 2 in the technical review).

Question 3

The search strategy retrieved 592 articles, of which 162 were duplicates. The remaining 430 references went to the title and abstract screening stage. Then, 80 were included for full-text screening. A total of 3 primary studies proved eligible (see Figure 3 in the technical review).

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Quality of Evidence

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Very low	The Committee has very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Methods Used to Analyze the Evidence

Meta-Analysis

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Data Extraction and Analysis

Using a piloted form, data extraction was conducted by one researcher and a second reviewer checked for accuracy. The information retrieved from primary studies included their main features, type of design, patient characteristics, clinical and histological definition of microscopic colitis (MC), risk of bias assessment, and outcomes measured.

When feasible, contingency tables were created for each dichotomous outcome, and the relative risk (RR) and its 95% confidence interval (CI)

was calculated. When data from intention-to-treat analysis were shown, this was preferred over per-protocol analysis. The only exception to this was the outcome of adverse events, for which per-protocol analysis was performed. For continuous outcomes, the mean difference (MD) and its 95% CI was calculated. To facilitate decision making, the data from studies reporting clinical relapse during the maintenance period were transformed from the number of patients free from relapse to the number of participants having the event. When aggregated data such as standard deviation for a group were missing, the exact *P* value was used to approximate it. A random effects model was chosen a priori given that different dosages and methods of administration of medications were expected, representing a distribution of results of effectiveness. Review Manager 5.3 software (Nordic Cochrane Centre, Cochrane Collaboration, Copenhagen, Denmark) was used to conduct the meta-analyses.

Risk of Bias Assessment of Included Studies

To determine the risk of bias of included studies, the Cochrane Risk of Bias Tool for randomized controlled trials and diagnostic test accuracy studies were used. For randomized controlled trials, the following domains were considered: (1) Was the random sequence adequately generated? (2) Was the allocation adequately concealed? (3) Were participants blinded to the intervention received? (4) Were personnel blinded to the intervention administered? (5) Were outcome adjudicators blinded to the intervention administered? (6) Was the study affected by incomplete outcome data? (7) Was the study affected by selective outcome reporting? (8) Was any other additional bias identified? The domains considered to assess the risk of bias of diagnostic test accuracy were as follows: (1) Was the spectrum of patients representative of the patients who will receive the test in practice? (2) Is the reference standard likely to classify the target condition correctly? (3) Is the time period between the reference standard and the index test short enough to be reasonably sure that the target condition did not change between the 2 tests? (4) Did the whole sample, or a random selection of the sample, receive verification using the intended reference standard? (5) Did patients receive the same reference standard irrespective of the index test result? (6) Was the reference standard independent of the index test (i.e., the index test did not form part of the reference standard)? (7) Were the results of the reference standard interpreted without knowledge of the results of the index test? (8) Were the results of the index test interpreted without knowledge of the results of the reference standard? (9) Were the same clinical data available when test results were interpreted as would be available when the test is used in practice? (10) Were withdrawals from the study explained? This assessment was conducted in duplicate by 2 independent evaluators.

Evaluation of the Quality of the Body of Evidence

The quality of the body of evidence (also known as confidence or certainty in the evidence) across outcomes was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. In this approach, randomized controlled trials start as high-quality evidence; however, the confidence in the estimates of effect can be downgraded from high to moderate, low, or very low when serious or very serious issues related to risk of bias, imprecision, indirectness, inconsistency, and publication bias are identified. For diagnostic test accuracy studies using a cross-sectional design, the quality of the evidence starts as high and the same domains were assessed to determine whether downgrading was necessary. Results were tabulated using evidence profiles and evidence to decision tables. The Guideline Development Tool (GDT) software was used to assess and record judgments related to the quality of evidence assessment and move from the evidence to decisions (www.guidelinedevelopment.org).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The American Gastrointestinal Association (AGA) process for developing clinical practice guidelines incorporates best practices of guideline development as outlined by the Institute of Medicine. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach was used to prepare the background summary of evidence, develop the technical review, and assess the certainty of the evidence and grade the strength of the recommendations. Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The guideline panel and the authors of the technical review met in person on April 25, 2015, to discuss the quality of evidence (see Table 1 in the original guideline document) and consider other factors relevant for the risk/benefit assessment of the recommendations. The guideline authors subsequently formulated the recommendations. Although quality of evidence was a cardinal factor in determining the strength of the recommendations (see Table 2 in the original guideline document), the balance between benefit and harm, patients' values and preferences, and resource utilization was also taken into consideration.

Rating Scheme for the Strength of the Recommendations

Grading of Recommendations Assessment, Development and Evaluation (GRADE) Definitions of Strength of Recommendation

	For the Patient	For the Clinician
Strong	Most individuals in this situation would want the recommended course of action and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on the medical management of microscopic colitis. The guideline was developed by the AGA Clinical Guidelines Committee and approved by the AGA Governing Board.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

- A meta-analysis of 6 randomized clinical trials showed clear benefit of budesonide in inducing clinical response, with 5 studies also showing histological response. Two studies also showed improvement in quality of life, although the difference did not reach statistical significance. Patients treated with 9 mg of budesonide daily were more than twice as likely to achieve clinical remission over an average of 7 to 13 days when compared with no treatment (relative risk [RR], 2.52; 95% confidence interval [CI], 1.45–4.4).
- In a single randomized controlled trial, 44% of 16 patients treated with Boswellia serrata improved clinically compared with 27% of 15 patients in the placebo arm, and there was no difference in quality of life between the 2 groups.

Potential Harms

- It is unknown whether long-term treatment of bismuth salicylate would be associated with salicylate or bismuth toxicity. Moreover, taking 8 to 9 bismuth salicylate tablets divided 3 times daily imposes a significant pill burden on an older patient population that frequently takes multiple medications.
- Although the quality of the evidence for safety data was very low, extensive clinical experience with systemic corticosteroids for other

conditions suggests that the risk of adverse events is significant.
- Although the systemic bioavailability of budesonide is low, prolonged use may predispose to bone loss. Thus, osteoporosis prevention and screening should be considered in patients who require maintenance therapy.

Qualifying Statements

Qualifying Statements

Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Clinical Algorithm

Patient Resources

Staff Training/Competency Material

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Identifying Information and Availability

Bibliographic Source(s)

Nguyen GC, Smalley WE, Vege SS, Carrasco-Labra A, Clinical Guidelines Committee. American Gastroenterological Association Institute guideline on the medical management of microscopic colitis. Gastroenterology. 2016 Jan;150(1):242-6. [9 references] PubMed

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2016 Jan

Guideline Developer(s)

American Gastroenterological Association Institute - Medical Specialty Society

Source(s) of Funding

American Gastroenterological Association Institute

Guideline Committee

American Gastroenterological Association Institute Clinical Guidelines Committee

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Financial Disclosures/Conflicts of Interest

Conflicts of Interest

All guideline panel members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and pertinent disclosures are published with the report.

Guideline Status

This is the current release of the guideline.

This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Gastroenterology Journal Web site.

Availability of Companion Documents

The following are available:

- American Gastroenterological Association Institute technical review on the medical management of microscopic colitis. Gastroenterology. 2016 Jan;150(1):247-74. Available from the Gastroenterology Journal Web site.
- AGA Institute guideline on the management of microscopic colitis: clinical decision support tool. Gastroenterology. 2016 Jan;150(1):276. Available from the Gastroenterology Journal Web site.
- AGA process for developing guidelines. 2014 Dec. Available from the American Gastroenterological Association (AGA) Web site.
- The AGA Institute process for developing clinical practice guidelines part one: grading the evidence. Clin Gastroenterol Hepatol. 2013 Apr;11(4):329-32. Available from the Clinical Gastroenterology and Hepatology Web site.

The guideline also has an accompanying continuing medical education (CME) activity available from the Gastroenterology Journal Web site.

Patient Resources

The following is available:

- Managing microscopic colitis: a patient guide. Gastroenterology 2016 Jan;150(1):275. Available from the Gastroenterology Journal Web site.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC Status

This NGC summary was completed by ECRI Institute on May 5, 2016. The information was verified by the guideline developer on June 3, 2016.

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